

## Adverse drug reactions

## Pharmacogenetics and adverse drug reactions

Urs A Meyer

**Polymorphisms in the genes that code for drug-metabolising enzymes, drug transporters, drug receptors, and ion channels can affect an individual's risk of having an adverse drug reaction, or can alter the efficacy of drug treatment in that individual. Mutant alleles at a single gene locus are the best studied individual risk factors for adverse drug reactions, and include many genes coding for drug-metabolising enzymes. These genetic polymorphisms of drug metabolism produce the phenotypes of "poor metabolisers" or "ultrarapid metabolisers" of numerous drugs. Together, such phenotypes make up a substantial proportion of the population. Pharmacogenomic techniques allow efficient analysis of these risk factors, and genotyping tests have the potential to optimise drug therapy in the future.**

The person-to-person variability of a drug response is a major problem in clinical practice and in drug development. It can lead to therapeutic failure or adverse effects of drugs in individuals or subpopulations of patients. The occurrence of serious or fatal adverse drug reactions has been extensively analysed in hospital inpatients. A meta-analysis of 39 prospective studies from US hospitals suggests that 6.7% of inpatients have serious adverse drug reactions and 0.32% have fatal reactions, the latter causing about 100 000 deaths per year in the USA. This figure makes adverse drug reactions between the fourth and sixth leading causes of death in hospital inpatients.<sup>1</sup>

What determines an individual's risk of developing an adverse drug reaction or of gaining no benefit from the drug? How much of this pharmacological variability can be predicted? How many adverse drug reactions can thereby be prevented? These are some of the questions addressed in this review.

Potential risk factors for drug inefficacy or toxicity include drug-drug interactions, the patient's age, renal and liver function or other disease factors, and lifestyle variables such as smoking and alcohol consumption. Of even greater importance in the determination of individual risk are inherited factors that affect the kinetics and dynamics of numerous drugs. Thus, genetic variation in genes for drug-metabolising enzymes, drug receptors, and drug transporters have been associated with individual variability in the efficacy and toxicity of drugs.<sup>2-6</sup> It is of course difficult to disentangle the contribution of environmental and genetic factors in an individual patient. A major difference between genetic and environmental variation is that an inherited mutation or trait is present throughout life and has to be tested for only once in a lifetime, whereas environmental effects are continually changing. If mutant or variant genes exist at a frequency of more than 1% in the normal population, they are called genetic polymorphisms.<sup>2</sup> Genetic polymorphisms explain why a small proportion of the population may be at higher risk of drug inefficacy or toxicity; the study of such polymorphisms has given rise to the field of pharmacogenetics.<sup>3-6</sup>

*Lancet* 2000; **356**: 1667-71

Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, CH-4056 Basel, Switzerland (U A Meyer MD)  
(e-mail: Urs.A.Meyer@unibas.ch)

## History of pharmacogenetics

Pharmacogenetics had its beginning in the 1950s when researchers realised that some adverse drug reactions could be caused by genetically determined variations in enzyme activity. For example, prolonged muscle relaxation after suxamethonium was explained by an inherited deficiency of a plasma cholinesterase, and haemolysis caused by antimalarials was recognised as being caused by inherited variants of glucose-6-phosphate dehydrogenase. Similarly, inherited changes in a patient's ability to acetylate isoniazid was found to be the cause of the peripheral neuropathy caused by this drug. More recently, adverse drug reactions such as nausea, diplopia, and blurred vision after the antiarrhythmic and oxytocic drug sparteine, or incapacitating orthostatic hypotension after the antihypertensive agent debrisoquine have led to the discovery of the genetic polymorphism of the drug-metabolising enzyme cytochrome P450 2D6 (CYP2D6).<sup>7</sup> Adverse drug reactions were also the clinical events that revealed genetic variants of other drug-metabolising enzymes or drug targets, a selection of which is listed in table 1.<sup>3,8-12</sup> Thus, genetic polymorphisms were discovered by incidental observations that some patients or volunteers experienced unpleasant and disturbing adverse drug reactions when given standard doses of drugs.

## Genotype and phenotype

Molecular genetics and genomics (the study of the entire set of human genes) have transformed pharmacogenetics in the past decade. The two alleles carried by an individual at a given gene locus, referred to as the genotype, can now be characterised at the DNA level; their influence on the kinetics of the drug or a receptor function, the phenotype, can be measured by advanced analytical methods for metabolite detection or by sophisticated clinical investigations—eg, receptor-density studies by positron emission tomography. Molecular studies in pharmacogenetics started with the cloning and characterisation of CYP2D6,<sup>7,13</sup> and have now been extended to numerous other human genes, including those coding for more than 20 drug-metabolising enzymes and drug receptors, and several drug transport systems ([www.sciencemag.org/feature/data/1044449.shl](http://www.sciencemag.org/feature/data/1044449.shl)).

More than 70 variant alleles of the CYP2D6 locus have been described ([www.imm.ki.se/CYPalleles/cyp2d6.htm](http://www.imm.ki.se/CYPalleles/cyp2d6.htm)), of which at least 15 encode non-functional gene

| Enzyme                          | Frequency of polymorphism                                     | Drug                                      | Drug effect  |
|---------------------------------|---|---|--|
| CYP2C9                          | 14–28% (heterozygotes)<br>0–2–1% (homozygotes)                | Warfarin                                  | Haemorrhage <sup>8</sup>   |
|                                 |   | Tolbutamide                               | Hypoglycaemia <sup>9</sup>   |
|                                 |   | Phenytoin                                 | Phenytoin toxicity <sup>10</sup>   |
|                                 |   | Gilipizide                                | Hypoglycaemia <sup>10</sup>  |
|                                 |   | Losartan                                  | Decreased antihypertensive effect <sup>8</sup>                                     |
| CYP2D6                          | 5–10% (poor metabolisers)<br>1–10% (ultra-rapid metabolisers) | Antiarrhythmics                           | Proarrhythmic and other toxic effects <sup>3</sup>                                 |
|                                 |   | Antidepressants                           | Toxicity in poor metabolisers, inefficacy in ultrarapid metabolisers <sup>2</sup>  |
|                                 |   | Antipsychotics                            | Tardive dyskinesia <sup>2</sup>  |
|                                 |   | Opioids                                   | Inefficacy of codeine as analgesic, narcotic side-effects, dependence <sup>3</sup> |
|                                 |   | $\beta$ -adrenoreceptor antagonists       | Increased $\beta$ -blockade <sup>3</sup>   |
| CYP2C19                         | 3–6% (whites)<br>8–23% (Asians)                               | Omeprazole                                | Higher cure rates when given with clarithromycin <sup>11</sup>                     |
|                                 |   | Diazepam                                  | Prolonged sedation <sup>3</sup>  |
| Dihydropyrimidine dehydrogenase | 0–1%  | Fluorouracil                              | Neurotoxicity, myelotoxicity <sup>12</sup>   |
| Plasma pseudocholinesterase     | 1–5%  | Succinylcholine                           | Prolonged apnoea <sup>3</sup>  |
| N-acetyltransferase             | 40–70% (whites)<br>10–20% (Asians)                            | Sulphonamides                             | Hypersensitivity <sup>2</sup>  |
|                                 |   | Amonafide                                 | Myelotoxicity (rapid acetylators) <sup>12</sup>                                    |
|                                 |   | Procainamide, hydralazine, isoniazid      | Drug-induced lupus erythematosus <sup>3</sup>                                      |
| Thiopurine methyltransferase    | 0–3%  | Mercaptopurine, thioguanine, azathioprine | Myelotoxicity <sup>12</sup>  |
| UDP-glucuronosyl transferase    | 10–15%  | Irinotecan                                | Diarrhoea, myelosuppression <sup>12</sup>  |

Table 1: Clinically important genetic polymorphisms of drug metabolism that influence drug response

products. These alleles are different from the normal (wild-type) gene by one or more point mutations, but also include gene deletions and gene duplications or multiduplications. The mutations can have no effect on enzyme activity, or can code for enzymes with decreased or absent activity; duplications lead to increased enzyme activity. Extensive metabolisers are defined as individuals homozygous or heterozygous for the wild-type or normal activity enzymes (75–85% of the population); intermediate metabolisers (10–15%)<sup>14</sup> or poor metabolisers (5–10%) are carriers of two decreased-activity alleles or loss-of-function alleles; and ultrarapid metabolisers (1–10%) are carriers of duplicated or multiduplicated active genes.<sup>4,7</sup> Although the number and complexity of the mutations may be large overall, only a few mutant genes, usually three to five alleles, are common and account for most (usually >95%) of mutant alleles. These alleles can be detected by modern DNA methods, including DNA chip microarrays, allowing most patients to be assigned to a particular phenotype group.

CYP2D6 remains one of the best studied polymorphic genes of pharmacological interest; numerous other genes have been or are presently being studied by identical approaches. The poor-metaboliser phenotype for most of the polymorphic genes is inherited as an autosomal recessive trait, requiring the presence of two mutant alleles. These considerations apply to monogenic traits, where one gene has a major effect on the phenotype and divides the population into two or three distinct groups. However, the responses to most medications are not monogenic but involve the interaction between multiple

gene products involved in drug disposition and drug action. Polygenic inheritance is more difficult to detect and to distinguish from environmental factors. The analysis of polygenic inheritance is similar to the analysis of complex diseases such as cancer, mental diseases, arthritis, and asthma, in which primary genes, modifier genes, and environmental factors interact.<sup>6,15</sup>

A simple method to distinguish between hereditary and environmental components of variability is the comparison of small series of monozygotic and dizygotic twins, or repeated drug administration and comparison of the variability of the responses within and between individuals as proposed by Kalow.<sup>16</sup> The techniques have revealed important genetic factors in the pharmacokinetics of drugs such as dicoumarol, halothane, phenytoin, tolbutamide, and midazolam.

In the future, the discovery of pharmacogenetic traits will change with the new technologies based on genomics. Rapid sequencing and single-nucleotide polymorphisms (SNPs) will have a major role in the linking of sequence variations with heritable clinical phenotypes of drug response. SNPs occur in about one of every 100–1500 bp of the genomes if two unrelated individuals are compared. Any two individuals therefore differ by about 3 million bp—ie, in only about 0.1% of the 3 billion bp of the haploid genome. Common or informative SNPs are those that occur at frequencies of greater than 1%, or even better, of greater than 10%. Once a large number of these SNPs and their frequencies in different populations are known, they can be used to correlate a patient's genetic "fingerprint" with the probable individual drug response.<sup>6,15</sup> SNPs in coding regions of genes (about 30 000–100 000 per genome) can cause aminoacid changes and changes in protein function, or they can be neutral. SNPs inside genes or in regulatory regions can cause differences in protein expression. The proteomes of two individuals can differ by only 30 000 proteins, and some of these differences might affect drug response. The ability to predict interindividual differences in drug efficacy or toxicity on the basis of genetic factors will thus be a realistic scenario for future drug treatments.

### Population differences in pharmacogenetic traits

All pharmacogenetic variations studied to date occur at different frequencies among subpopulations of different ethnic or racial origin. For instance, important cross-ethnic differences exist in the frequency of slow acetylators of isoniazid due to mutations of N-acetyltransferase 2, of poor metabolisers due to mutations of CYP2C9 and CYP2C19, and of ultrarapid metabolisers due to mutations of CYP2D6 (table 2).<sup>4,7</sup> Some of the mutations of these genes occur uniquely in certain ethnic subpopulations. This ethnic diversity, also called "gene geography", implies that ethnic origin has to be considered in pharmacogenetic studies and in pharmacotherapy.

### Therapeutic issues

In principle, three pharmacogenetic mechanisms can influence pharmacotherapy. The first and best studied to date are genetic polymorphisms of genes that are associated with altered metabolism of drugs (eg, metabolism of tricyclic antidepressants). Increased or decreased metabolism of a drug can change the concentrations of that drug, as well as those of its active, inactive, or toxic metabolites. Second, genetic variants can produce an unexpected drug effect (eg, haemolysis

|                                | Genotype  | Frequency  |            |                   |                             |
|--------------------------------|---|------------|------------|-------------------|-----------------------------|
|                                |   | Whites     | Asians     | Black Africans    | Ethiopians & Saudi Arabians |
| <b>Poor metabolisers</b>       |   |            |            |                   |                             |
| CYP2C9                         | Homozygous or compound heterozygous for CYP2C9*2 or *3                      | 0.2–1.0%   | ND         | ND                | ND                          |
|                                | Heterozygous for CYP2C9*2 or *3 (decreased activity)                        | 14.0–37.0% | 2.0–3.0%   | 0.5%              | ND                          |
| CYP2D6                         | Homozygous or compound heterozygous for numerous loss-of-function alleles   | 5.0–13.5%  | 0.0–1.0%   | 0.0–8.1% (18.7%)* | 1.8–2.0%                    |
| <b>Ultrarapid metabolisers</b> |   |            |            |                   |                             |
| CYP2D6                         | Gene duplication or multiduplication (dominant)                             | 1.0–10.0%  | 0.0–2.0    | 2.0%              | 10.0–29.0%                  |
| <b>Slow acetylators</b>        |   |            |            |                   |                             |
| N-acetyltransferase 2          | Homozygous or compound heterozygous for numerous decreased-function alleles | 40.0–70.0% | 10.0–20.0% | 50.0–60.0%        | ND                          |

ND=not determined. \*In San bushmen.

Table 2: Distribution of polymorphic genes encoding CYP2C9, CYP2D6, and N-acetyltransferase 2 in different populations

in glucose-6-phosphate dehydrogenase deficiency). Third, genetic variation in a drug target can alter the clinical response and frequency of side-effects (eg, variants of the  $\beta$ -adrenergic receptor alter response to  $\beta$ -agonists in asthma patients).

Whether a genetic polymorphism has relevance for drug therapy mainly depends on the characteristics of the drug in question. The quantitative role of a drug-metabolising enzyme, or a drug-uptake mechanism in the overall kinetics of a drug and the agent's therapeutic range will determine how much the dose has to be adjusted in poor metabolisers or ultrarapid metabolisers. The example of the CYP2D6 polymorphism again provides incontrovertible clinical evidence for these ideas. Most patients (about 90%) require 75–150 mg/day of nortriptyline to reach a "therapeutic" plasma steady-state concentration of 200–600 nmol/L, but poor metabolisers need only 10–20 mg/day to reach the same concentrations. Ultrarapid metabolisers, on the other hand, may require 300–500 mg/day or even more to reach the same plasma concentration (figure).<sup>17,18</sup> Obviously, if the genotype or phenotype of the patient is not known, poor metabolisers will be overdosed and be at high risk of drug toxicity, whereas ultrarapid metabolisers will be underdosed.

Another situation is presented if the therapeutic effect depends on the formation of an active metabolite (eg, morphine from codeine). Poor metabolisers will have no drug effect and ultrarapid metabolisers may have exaggerated drug responses.<sup>19</sup> The drug-related criteria that make a genetic polymorphism clinically relevant are similar to those for drug-concentration monitoring—ie, narrow therapeutic range or large interindividual

variation in kinetics or suspicion of overdose. In pharmacogenetics, however, a single DNA test done once in a lifetime can identify the predisposition of patients, at least of those with extreme phenotypes.

### Examples of genetic polymorphisms affecting drug kinetics and drug toxicity

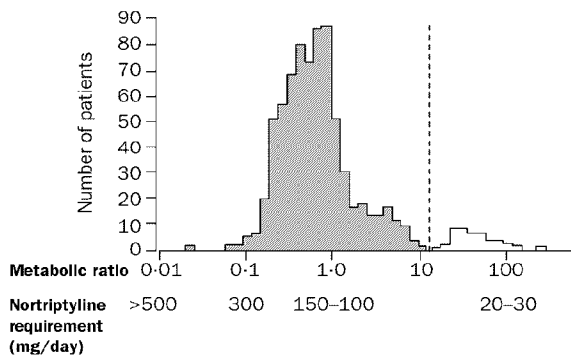
#### Drug metabolism

Many or most of the 50–100 drug-metabolising enzymes known are subject to common genetic polymorphisms. Table 1 lists some in which clinically important differences in drug response have been documented. As an example, there is substantial interindividual variation in plasma concentrations of antidepressants.<sup>3,17</sup>

CYP2D6—The metabolism of the tricyclic antidepressants amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline, and of the tetracyclic compounds maprotiline and mianserin is influenced by the CYP2D6 polymorphism to various degrees. For these agents, there are therefore two groups of patients that may pose clinical problems.

The poor metabolisers (and to a lesser degree the intermediate metabolisers) predictably have increased plasma concentrations of tricyclic antidepressants when given recommended doses of the drugs. The other group are the ultrarapid metabolisers who are prone to therapeutic failure because the drug concentrations at normal doses are far too low (figure). 5–20% of patients can belong to one of these risk groups, depending on the population studied. Adverse effects clearly occur more frequently in poor metabolisers and may be misinterpreted as symptoms of depression and lead to erroneous further increases in the dose.

In addition to antidepressants, many other drugs used in psychiatry are affected by the CYP2D6 polymorphism. The metabolism of the recently introduced antidepressant venlafazine is controlled by CYP2D6, and poor metabolisers have a substantially decreased oral clearance and increased cardiovascular toxicity.<sup>20</sup> This effect has been documented, however, in only a few patients so far. Another group of antidepressants are the selective serotonin reuptake inhibitors which interact with CYP2D6 in three different ways. Paroxetine, fluvoxamine, and fluoxetine are in part metabolised by CYP2D6. However, the phenotype differences in clearance or plasma concentrations are small in relation to the relatively large therapeutic index of these drugs. Of substantial importance is the ability of these agents to act as potent competitive inhibitors of CYP2D6 (paroxetine, fluoxetine). Such inhibition means that the elimination of other CYP2D6 substrates—eg, of tricyclic antidepressants—is impaired, and that phenotyping with



#### Dose requirement for nortriptyline in patients with different CYP2D6 phenotypes<sup>17,18</sup>

Poor metabolisers are defined as individuals with a debrisoquine urinary metabolic ratio of >12.6 (dashed line).

| Gene   | Frequency | Drug   | Drug effect   |
|--|-----------|--|---|
| Multidrug resistance gene ( <i>MDR1</i> ) <sup>20</sup>                            | 24%       | Digoxin  | Increased concentrations of digoxin in plasma       |
| $\beta_2$ adrenergic receptor gene ( <i><math>\beta_2</math>AR</i> ) <sup>20</sup> | 37%       | Albuterol                                      | Decreased response to $\beta_2$ adrenergic agonists |
| Sulphonylurea receptor gene ( <i>SUR1</i> )  | 2–3%      | Tolbutamide                                    | Decreased insulin response                          |
| LQT 1–5 mutations on five genes coding for cardiac ion channels) <sup>27</sup>     | 1–2%      | Antiarrhythmics, terfenadine, many other drugs | Sudden cardiac death due to long-QT syndrome        |

Table 3: Clinically important genetic polymorphisms of drug targets and drug transporters

debrisoquine, sparteine, or dextromethorphan results in false positive results or “phenocopies” of poor metabolisers, if serotonin-selective reuptake inhibitors are coadministered. These interactions are phenotype-dependent—ie, restricted to extensive metabolisers. Citalopram, fluvoxamine, and sertraline do not share this inhibitory property and do not cause CYP2D6-specific interactions. Fluvoxamine is also a substrate and potent inhibitor of CYP1A2, and thus causes important interactions with drugs that are partly metabolised by this cytochrome P450 enzyme, such as amitriptyline, clomipramine, imipramine, clozapine, and theophylline. Thus, polymorphic drug metabolism affects a large number of drugs used in psychiatric patients, raising the question of how this information will be used by physicians in the future. Retrospective analysis of psychiatric patients treated with substrates of CYP2D6 strongly indicates that genotyping can improve efficacy, prevent adverse drug reactions, and decrease costs of therapy with these agents.<sup>21</sup> Obviously, prospective trials are needed to prove the value of phenotyping or genotyping patients with depression in selecting the proper starting dose to increase therapeutic efficacy and prevent toxicity. Striking differences in the adverse drug reactions of opioids are associated with the *CYP2D6* polymorphism. Dextromethorphan, codeine, hydrocodone, oxycodone, ethylmorphine, and dihydrocodeine are dealkylated by polymorphic CYP2D6. The polymorphic O-demethylation of codeine is of clinical importance when this drug is given as an analgesic. About 10% of codeine is O-demethylated to morphine, and this pathway is deficient in poor metabolisers. Poor metabolisers therefore experience no analgesic effects of codeine.<sup>3,19</sup> Similarly, respiratory, psychomotor, and pupillary effects of codeine are decrease in poor metabolisers compared with extensive metabolisers. Codeine is frequently recommended as a drug of first choice for treatment of chronic severe pain. Physicians must appreciate that no analgesic effect is to be expected in the 5–10% of whites who are of the poor metaboliser phenotype, or who are extensive metabolisers and receive concomitant treatment with a potent inhibitor of CYP2D6 such as quinidine. The inability to form active metabolites from opioids could protect poor metabolisers against oral opiate dependence.

*CYP2C9*—Another example of a clinically important genetic polymorphism of drug metabolism is the association of variant alleles of *CYP2C9* with lower warfarin dose requirements. In a retrospective study of a population from an anticoagulant clinic, the *CYP2C9* alleles associated with decreased enzyme activity (\*2 and \*3) were found to be over-represented in patients stabilised on low doses of warfarin. These patients had an increase incidence of major and minor haemorrhage.\* Up to 37% of a British population were carriers of one mutant allele (\*2 or \*3) and were therefore at higher risk

of haemorrhage (table 2). Homozygous carriers of mutant alleles of *CYP2C9* are rare (0.2–1.0% of the population) and this genotype is associated with an even higher risk of warfarin adverse drug reactions and with severe impairment of the metabolism of tolbutamide, glipizide, and phenytoin.<sup>9,10</sup>

*Cancer chemotherapy*—The severe and potentially fatal bone-marrow toxicity (acute leucopenia, anaemia, and pancytopenia) in patients with thiopurine methyltransferase deficiency treated with standard doses of mercaptopurine, thioguanine, and azathioprine is a rare (about one in 300) event in the treatment of acute lymphoblastic leukaemia in children. Patients with this purine methyltransferase deficiency can require up to a 15-fold reduction in mercaptopurine to prevent fatal haematotoxicity.<sup>5,12,22</sup> Other pharmacogenetic examples of adverse drug reactions in cancer chemotherapy are the myelosuppression and neurotoxicity of fluorouracil in patients with a deficiency of dihydropyrimidine dehydrogenase; the myelosuppression and diarrhoea after the topoisomerase I inhibitor irinotecan in patients with an inherited deficiency in glucuronidation by a promoter polymorphism of UGT-glucuronosyltransferase UGT1A1; and the greater bone-marrow toxicity of the topoisomerase II inhibitor amonafide in N-acetyltransferase 2 rapid acetylators (30–60% of whites, 80–90% of Asians).<sup>5,12</sup>

#### Drug transport

Several membrane transporters are involved in the absorption of drugs into the intestinal tract, in the uptake into the brain and other tissues, or in the transport into specific sites of action—eg, the synaptic cleft. However, little is known about transporter variants in relation to drug response. One such variant was recently discovered for the multidrug resistance gene *MDR1*, which codes for an ATP-dependent transmembrane efflux pump (P-glycoprotein), whose function is the export of numerous substances including drugs from the inside of cells to the outside, protecting cells from accumulation of toxic substances or metabolites. A mutation in exon 26 of the *MDR1* gene (C3435T) correlated with the expression levels and the function of intestinal P-glycoprotein. Thus, the concentrations of digoxin in plasma were up to four-fold higher in individuals homozygous for this mutation after a single oral dose of digoxin. The maximum concentration in plasma ( $C_{max}$ ) of digoxin was also increased after chronic administration.<sup>23</sup> Homozygosity for this variant was observed in 24% of a German population. Substrates of P-glycoprotein include numerous important drugs with narrow therapeutic ranges including chemotherapeutic agents, ciclosporin A, verapamil, terfenadine, fexofenadin, and most HIV-1 protease inhibitors. Therefore, this polymorphism could have a major impact on the requirement for individual dose adjustments for carriers of this mutation. Mutations of other transporters, particularly those involved in reuptake of serotonin, dopamine, and  $\gamma$ -aminobutyric acid (GABA) are presently being studied with regard to clinically relevant changes in drug response. Transporter pharmacogenetics is a rapidly developing field.

#### Drug targets

The effects of most drug are exerted via interaction of the compound with membrane receptors (about 50% of drugs), enzymes (about 30%), or ion channels (about

5%).<sup>24</sup> Many of the genes encoding these proteins exhibit polymorphisms which may alter drug response. Clinically relevant examples are summarised in table 3.<sup>23,25-27</sup> One of the best studied drug receptors is the  $\beta_2$  adrenergic receptor, and some of its mutations (eg, the common mutation Arg→Gly at aminoacid 16) are major determinants of the  $\beta_2$ -agonist bronchodilator response.<sup>25</sup> Similarly mutations in the angiotensin converting enzyme (ACE) gene have been proposed to account for differences in the response to ACE inhibitors, but the data from different studies remain controversial.<sup>28</sup> A combination of two mutations of the gene for a high-affinity sulphonylurea receptor lead to a 40% reduction in the insulin response to tolbutamide<sup>29</sup> and genetic polymorphisms of the 5-hydroxytryptamine (serotonin) receptor HTR2A could be associated with the response to clozapine in patients with schizophrenia.<sup>29</sup>

Mutations in five genes, each encoding structural subunits of cardiac ion channels, affect the risk of drug-induced long-QT syndrome—a potential cause of sudden cardiac death in young individuals without structural heart disease. The prevalence of long-QT syndrome is about one in 10 000. All five genes code for membrane ion channels affecting sodium or potassium transport and are influenced by antiarrhythmics and other drugs.<sup>27</sup>

## Outlook

The systematic identification and functional analysis of human genes is revolutionising the study of disease processes and the development and rational use of drugs. It enables physicians to make reliable assessments of an individuals' risk of acquiring a particular disease, raises the number and specificity of drug targets, and explains interindividual variation of the therapeutic effectiveness and toxicity of drugs. Mutant alleles at a single gene locus are the best studied individual risk factors for adverse drug reactions, including the genes for N-acetyltransferase, thiopurine methyltransferase, dihydropyrimidine dehydrogenase, and the cytochrome P450 enzymes. Genotyping can predict the extremes of phenotypes in these situations. However, less definable pharmacogenetic factors produce a phenotype together with other variant genes and with environmental factors (eg, smoking, diet, &c). Genomics is providing the information and technology to analyse these complex multifactorial situations and to obtain individual genotypic information. Awareness of inherited variations of drug responsiveness, which are constant throughout life, can lead to dose adjustment on the basis of the patient's genetic makeup and are likely to prevent adverse drug reactions.

This study was supported by the Swiss National Science Foundation.

## References

- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200–05.
- Meyer UA. Genotype or phenotype: the definition of a pharmacogenetic polymorphism. *Pharmacogenetics* 1991; **1**: 66–67.
- Meyer UA. Drugs in special patient groups: clinical importance of genomics in drug effects. In: Carruthers GS, Hoffmann BB, Melmon KL, Nierenberg DW, eds. New York: McGrawHill, 2000: 1179–205.
- Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes; an opportunity for individualized drug treatment. *Trends Pharmacol Sci* 1999; **20**: 342–49.
- Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999; **286**: 487–91.
- Roses AD. Pharmacogenetics and future drug development and delivery. *Lancet* 2000; **355**: 1358–61.
- Meyer UA, Zanger UM. Molecular mechanisms of genetic polymorphisms of drug metabolism. *Annu Rev Pharmacol Toxicol* 1997; **37**: 269–96.
- Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 1999; **353**: 717–19.
- Miners JP, Birkett DJ. Cytochrome P4502C9; an enzyme of major importance in human drug metabolism. *Br J Clin Pharmacol* 1998; **45**: 525–38.
- Kidd RS, Straughn AB, Meyer MC, Blaisdell J, Goldstein JA, Dalton JT. Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9\*3 allele. *Pharmacogenetics* 1999; **9**: 71–80.
- Furuta T, Ohashi K, Kobayashi K, et al. Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* 1999; **66**: 265–74.
- Iyer L, Ratain MJ. Pharmacogenetics and cancer chemotherapy. *Eur J Cancer* 1998; **34**: 1493–99.
- Gonzalez FJ, Skoda RC, Kimura S, et al. Characterization of the common genetic defect in humans deficient in debrisoquine metabolism. *Nature* 1988; **331**: 442–46.
- Raimundo S, Fischer J, Eichelbaum M, Griese E-U, Schwab M, Zanger UM. Elucidation of the genetic basis of the common "intermediate metabolizer" phenotype for drug oxidation by CYP2D6. *Pharmacogenetics* 2000; **10**: 1–5.
- Brookes AJ. The essence of SNPs. *Gene* 1999; **234**: 177–86.
- Kalow W, Tang B-K, Endrenyi L. Hypothesis: comparison of inter- and intra-individual variations can substitute for twin studies in drug research. *Pharmacogenetics* 1998; **8**: 283–89.
- Bertilsson L, Dahl M-L, Tybring G. Pharmacogenetics of antidepressants: clinical aspects. *Acta Psychiatr Scand* 1997; **96**: 14–21.
- Dalén P, Dahl M-L, Bernal Ruiz ML, Nordin J, Bertilsson L. 10 hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther* 1998; **63**: 444–52.
- Sindrup SH, Brosen K. The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* 1995; **5**: 335–46.
- Lessard E, Yessine M-A, Hamelin BA, O'Hara G, LeBlanc J, Turgeon J. Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. *Pharmacogenetics* 1999; **9**: 435–43.
- Chou WH, Yan F-X, De Leon J, et al. Extension of a pilot study: impact of the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol* 2000; **20**: 246–51.
- Weinshilboum RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol* 1999; **39**: 19–52.
- Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci USA* 2000; **97**: 3473–78.
- Drews J, Ryser S. The role of innovation in drug development. *Nat Biotechnol* 1997; **15**: 1318–19.
- Liggett SB. The pharmacogenetics of beta2-adrenergic receptors: relevance to asthma. *J Allergy Clin Immunol* 2000; **105**: 487–92.
- Hansen T, Echwald SM, Hansen L, et al. Decreased tolbutamide-stimulated insulin secretion in healthy subjects with sequence variants in the high-affinity sulphonylurea receptor gene. *Diabetes* 1998; **47**: 598–605.
- Priori SG, Barhanin J, Hauer RN, et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management parts I and II\*. *Circulation* 1999; **99**: 518–28.
- Navis G, van der Kleij FG, de Zeeuw D, de Jong PE. Angiotensin-converting enzyme gene 1/D polymorphism and renal disease. *J Mol Med* 1999; **77**: 781–91.
- Arranz MJ, Munro J, Sham P, et al. Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. *Schizophr Res* 1998; **32**: 93–99.